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THE EFFECT OF UDMH INJECTION ON COMPLEX AVOIDANCE BEHAVIOR IN THE JAVA MONKEY

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FOREWORD

This work was performed jointly by members of the 6571st Aeromedical Research Laboratory, Holloman AFB, New Mexico, and the 6570th Aerospace Medical Research Laboratories, Wright-Patterson AFB, Ohio. The research was conducted in support of Project 6302, "Toxic Hazards of Propellants and Materials," Task 630202,"Pharmacology-Biochemistry," for the Toxic Hazards Branch, Physiology Division, Biomedical Laboratory, 6570th Aerospace Medical Research Laboratories. The assistance of A/1C Robert D. Bush and A/1C Vernon Pegram, psychological aides, is acknowledged, as well as the assistance of Capt. Bobby Caraway, USAF, VC, and 1/Lt Richard Brown, USAF, VC. Acknowledgment is also extended to A/1C David S. Belski for the drafting work, to Miss Lee Mitchell for the art work, and to Miss Sylvia Echavarria for her excellent administrative and typing assistance.

The experiments reported herein were conducted according to the "Principles of Laboratory Animal Care" established by the National Society for Medical Research.

ABSTRACT

Four java monkeys were injected with 30 mg/kg of 1, 1-dimethylhydrazine (UDMH) and their performance on a four-component operant schedule was compared with their performance under control conditions. In every instance where a performance decrement occurred (9 out of a possible 32), there was also associated clinical illness in the form of hyperactivity, nausea, vomiting, or lethargy. One subject showed no impairment following the two UDMH injections, while another subject exhibited an impairment on all four tasks during the second replication; this suggests the range of individual reactivity to UDMH exposure, and that repeated severe exposure may cause serious decrement of performance. From these data, one may expect clinical signs of illness after 2 to 3 hours, a performance decrement or change after 3 to 3-1/2 hours, and recovery to pre-exposure level of functioning between six and nine hours.

PUBLICATION REVIEW

This Technical Documentary Report has been reviewed and is approved.

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INTRODUCTION

In a previous study on the effects of the rocket fuel 1, 1-dimethylhydrazine (UDMH) on learned behavior, it was found that java monkeys did not exhibit a statistically significant decrement in their performance on an R-S avoidance task when the dosage of UDMH was 30 mg/kg (Ref. 2). Because it was believed that additional behavioral information on the 30 mg/kg dosage level was necessary, a different and more difficult group of tasks was designed which would permit the sampling of other aspects of behavior. Essentially, four tasks were added to the R-S avoidance schedule which requires simple continuous motor behavior. These were designed to measure gross motor behavior, and visual and auditory response latency.

Therefore, the purpose of this research was to evaluate java monkey performance on the new series of tasks as affected by 30 mg/kg of UDMH.

METHODS

A. Subjects

The subjects were 4 adult male java monkeys weighing between 4.1 and 6.3 kilograms. All subjects were trained on the tasks to a stabilized performance level over a period of four months; the psychomotor training procedures are the subject of another report (Ref. 3).

B. Apparatus

The apparatus consisted of a Primate Jumping Box and a performance test panel that was mounted on one end of the Box. The Primate Jumping Box, which is described in detail elsewhere (Ref. 1), consisted of two platforms separated by a well. Each platform was 24 inches long and 24 inches wide and was located 22 inches above the well. The two platforms and well were capable of carrying independent electrical charges. The distances between the two proximal edges of the platforms were 42 inches. The well and platforms were enclosed on three sides by plywood and on the front and top by plexiglass. A speaker was mounted on the ceiling and the wooden floor of the Box was covered by saw dust.

The performance test panel was mounted at one end of the Jumping Box. This consisted of 6 stimulus-response keys (SRK's), 2 lights, and 2 levers. The SRK is a "pushbutton" lever and is described in detail elsewhere (Ref. 4). The top SRK contained 0.125 inch diameter holes to permit the presentation of a 256 cps tone at 80 db from a speaker mounted behind it. A blue lamp was mounted behind each of the remaining 5 SRK's. A red lamp was mounted above the right lever as a cue for the continuous avoidance task, and a blue lamp above the left lever as a cue for the discrete avoidance task.

C. Performance Schedule

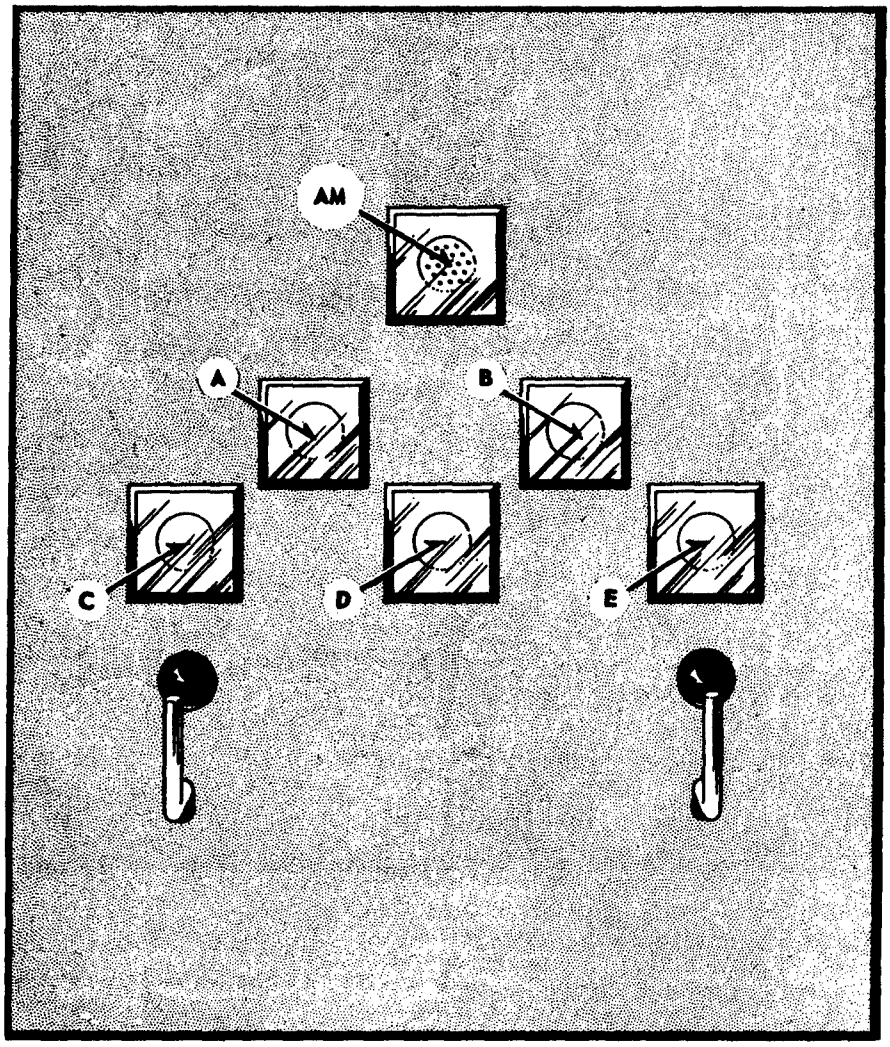
The performance schedule is the subject of another report (Ref. 3), but it will be described in brief here for ready reference.

When the red lamp was on above the right lever, the subject had to press the lever at least once every 15 seconds over a 3 minute period to avoid shock. At the same time as the subject was performing this task, the blue lamp above the left lever was turned on periodically. When this came on, the subject had 3 seconds in which to press the lever in order to

avoid shock. The lever pressing tasks, described elsewhere as continuous avoidance (CA) and discrete avoidance (DA) were the same as those employed during the Project Mercury animal flights (Ref. 5). At the same time as the subject was performing the CA/DA tasks, the tone and blue lights behind the SRK's were presented randomly and when these occurred the subject had 3 seconds to respond to the appropriate SRK. The temporal sequence of the stimulus events is presented in Figure 1. In response to a 8192 cps tone at 80 decibels, which emanated from the ceiling speaker, the subject was required to jump the 42 inches from one side of the jumping stand to the other. Failure to jump within 3 seconds resulted in the first grid becoming charged, and remaining charged until the subject was required to jump back from the opposing side, when the second grid became charged after 3 seconds. The subject made 4 jumps during each 2 minute rest period. Following the fourth jump, the 3 minute performance session was begun. Programming was accomplished with standard operant conditioning equipment. Performance data were obtained on a cumulative recorder, a response counter, and seven timers. The shock level was 6.5 ma. A test session of 13 minutes was employed (3' work - 2' rest - 3' work - 2' rest - 3' work), and the potential number of shocks an animal might be administered is shown in Table I. Table II provides information relative to the performance level of all subjects at the time testing began.

D. Procedure

After being restrained in a squeeze cage apparatus, control and experimental animals were injected at approximately 0730 and 0800, respectively. The subjects were injected intraperitoneally (I. P.), with the control subject receiving saline and the experimental subject receiving 30 mg/kg of UDMH. The control subject began work on the performance schedule at 0800 and on the hour thereafter, i.e., 0900, 1000, etc., while the experimental subject began work at 0830 and on the half hour thereafter, i.e., 0930, 1030, etc The schedule of experimentation required that each subject serve as a control



TEMPORAL SEQUENCE OF TASKS	
TASK	OCCURRENCE
Visual Monitoring	B C D A E
Auditory Monitoring	
Discrete Avoidance	
Continuous Avoidance	← continuous response required →
Time (seconds)	50 100 150

Figure 1. Performance Panel with Task Sequence

TABLE I

Potential Shocks During A 13-Minute Test Session

Performance Task	Potential Number of Shocks
Continuous Avoidance (CA)	36 - one shock possible every 15 seconds during each of the three 3-minute work periods (4 x 3 x 3).
Discrete Avoidance (DA)	9 - one shock possible for each presentation of the blue lamp over the left lever; 3 presentations during each 3 minute work period.
Visual Monitoring (VM)	15 - one shock possible for each presentation of any one of the five visual monitoring lights; 5 presentations during each 3-minute work period.
Auditory Monitoring (AM)	9 - one shock possible for each presentation of the auditory signal on the performance panel; 3 presentations during each 3-minute work period.
Gross Motor Response	11 - one shock for each jump required; 3 jumps before first 3 minutes work, and 4 jumps before each of the next two 3-minute work periods.

TABLE II

Level of Performance At Beginning of Testing
(13 Minute Work Session)

Subject #	Continuous Avoidance		Discrete Avoidance		Visual Monitoring		Auditory Monitoring	
	Mean Bar Presses/ Min	Standard Error of Mean	Mean Response Latency/ Sec	Standard Error of Mean	Mean Response Latency/ Sec	Standard Error of Mean	Mean Response Latency/ Sec	Standard Error of Mean
2	10.36	1.34	1.34	.27	.92	.92	.92	.14
4	11.74	.68	.64	.10	.64	.04	.73	.11
7	12.57	.79	1.13	.23	.85	.10	1.01	.20
8	7.56	.20	1.10	.18	.98	.09	.81	.16

the day prior to each of the two administrations of UDMH, and that the experimental treatments be separated by three consecutive days.

RESULTS

The results can best be presented by referring to each of the four subjects separately. Because of the individual differences in reaction, a group approach would not accurately convey the findings.

Subject #2

1st Control Test - After having been injected with saline at 0730, this subject performed at a considerably higher rate on the simple bar pressing task than he had during baseline studies. This noticeable enhancement is believed to have resulted from the procedure involved in preparing the animal for injection, i.e., restraint by a squeeze cage apparatus. Discrete avoidance, visual monitoring, and auditory monitoring behavior were of the usual quality throughout the day of testing. Figure 2 provides a graphic presentation of the data for this control day and also the data which resulted from subsequent experimentation with this subject.

1st UDMH Test - The subject was injected with UDMH at 0800 and at the 1030 performance session received one shock on the discrete avoidance task. At 1120, hyperactivity was observed in the home cage situation with the subject moving about in a restless fashion. On the following work session the subject again received one shock on the discrete avoidance task. For the remainder of the day, the subject received no shocks and was fully recovered by the seventh hour following injection. For this day of UDMH testing versus the preceding control day, it was found that both continuous avoidance and discrete avoidance behavior were significantly poorer

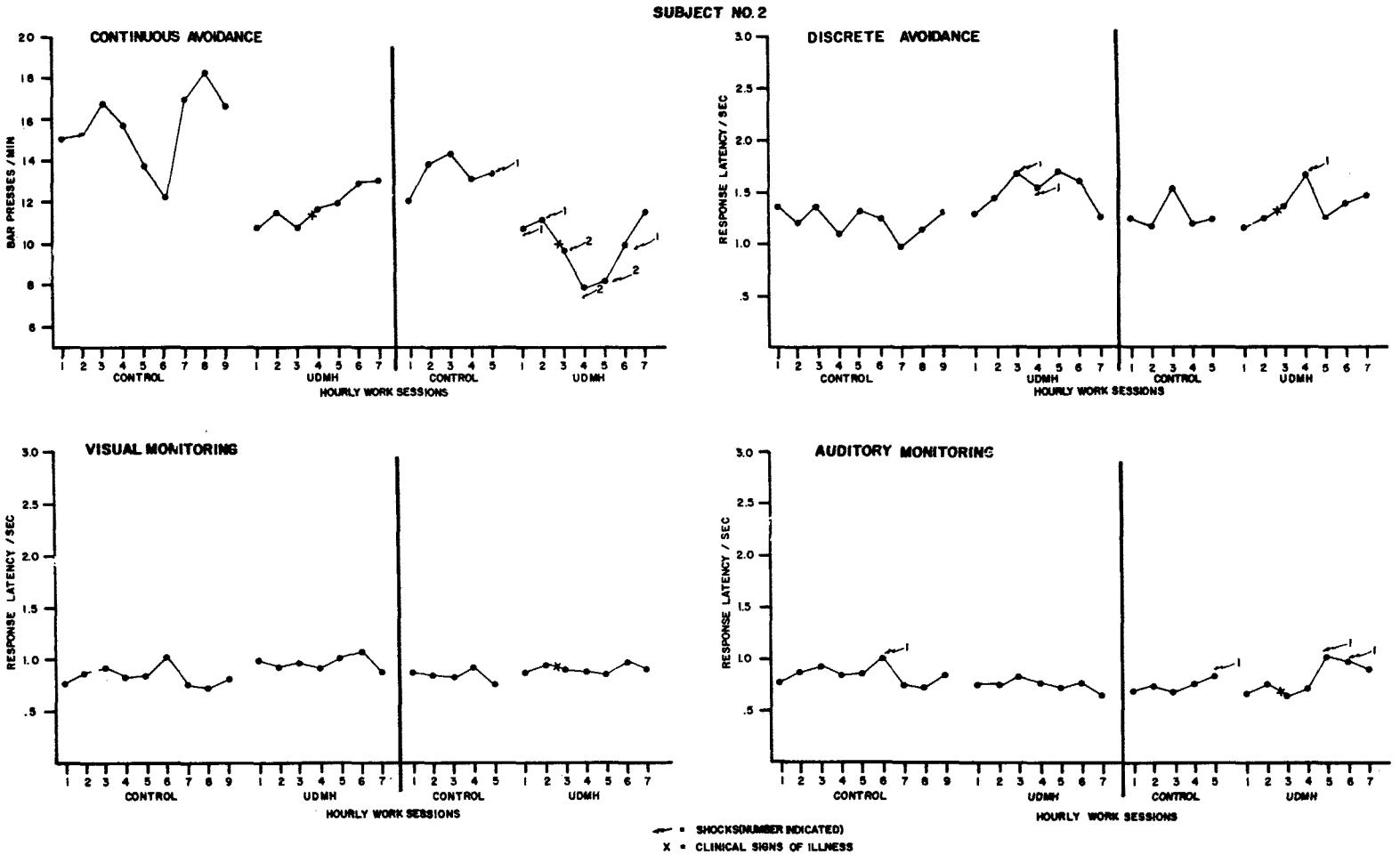


Figure 2. Control and Experimental Data (Subject 2)

($p < .01$). This comparison as well as all other statistical analyses for all subjects are provided in Tables III, IV, V, and VI.

2nd Control Test - After the 0730 injection of saline, the subject once again performed at a higher level on the simple bar pressing task than he had during baseline studies. With the exception of one shock received for slow auditory monitoring in the fifth work session of the day, all other tasks were performed without incident.

2nd UDMH Test - The subject received the injection of UDMH at 0800 and at 1030 hyperactivity was observed, followed at 1040 by some gagging. A significant decrement ($p < .01$) in performance of the simple bar pressing task was noted at 1130 hours with some evidence of a decrement in discrete avoidance and auditory monitoring. By the seventh hour following administration of UDMH the subject was fully recovered.

Subject #4

1st Control Test - The subject was injected with saline at 0730 and performed at a slightly lower rate on the continuous bar pressing task than he had previous to experimentation. This lowered rate resulted in 5 shocks over a five hour period out of a possible 180. All other parameters of performance were in line with previous experience. Figure 3 provides a graphic presentation of the data for this control day and also the data which resulted from subsequent experimentation with this subject.

1st UDMH Test - At 0800 the subject received the injection of UDMH and at the 1030 work session a decrement was noted on the continuous avoidance, visual monitoring, and auditory monitoring tasks, but these were not statistically significant. The subject was fully recovered by the end of the sixth hour of testing. No clinical signs of illness were noted throughout the day.

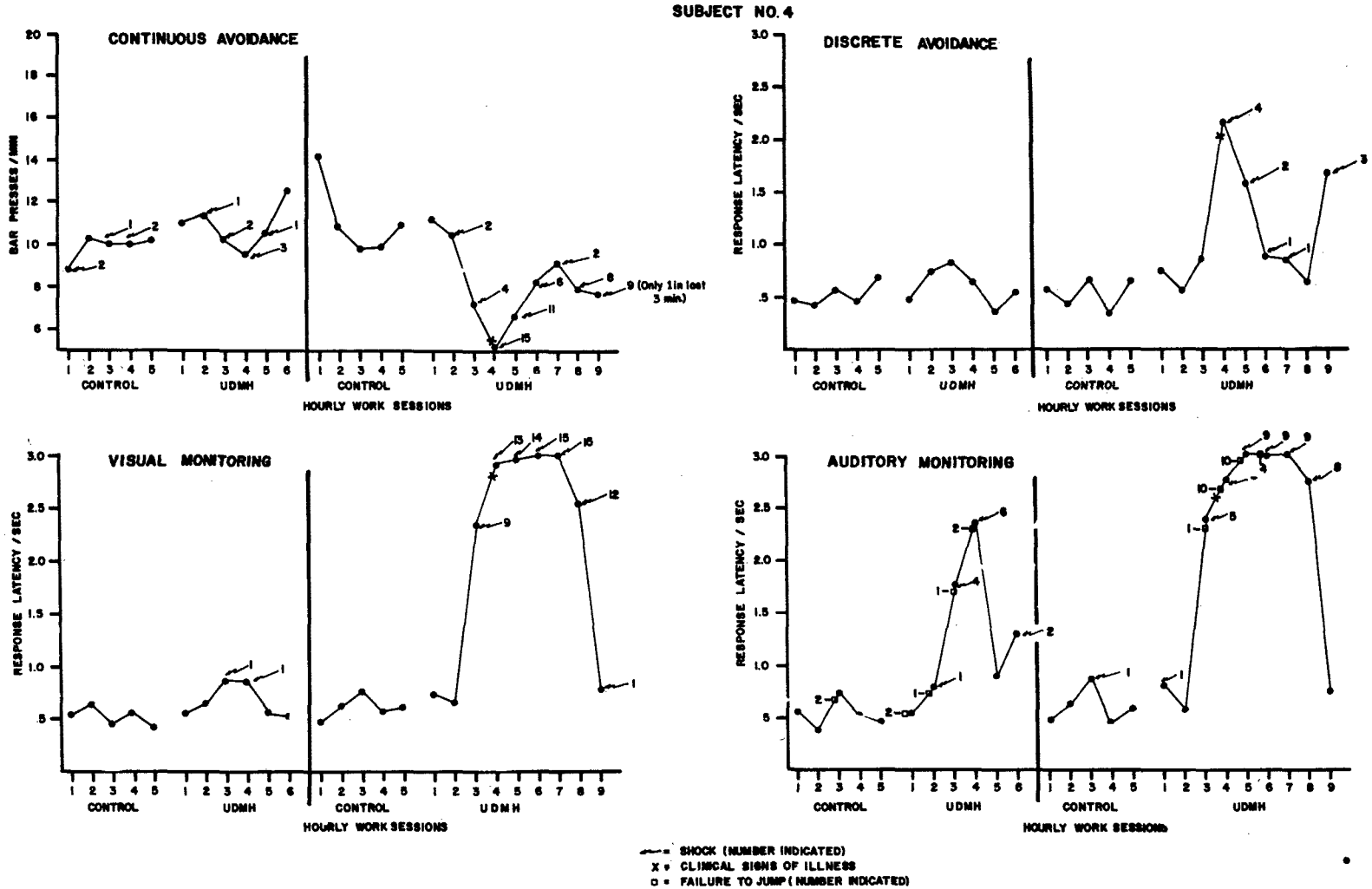


Figure 3. Control and Experimental Data (Subject 4)

2nd Control Test - The subject was injected with saline at 0730 and, except for a single shock during the third work session on auditory monitoring, performance was of baseline quality throughout the day.

2nd UDMH Test - UDMH was administered at 0800, and at 1026 the subject began coughing, with this followed by a small amount of vomitus. At 1030 the subject performed the behavioral tasks with considerable effort, failing to avoid 19 of 80 shocks. Performance on all tasks except discrete avoidance was impaired. Following this work session the subject was returned to his home cage, as usual, where he lay down and at 1104 vomited a small amount. At 1115 the subject coughed for approximately 30 seconds, producing only a very small amount of vomitus. The next work session was begun at 1130 and on the first jump cue the subject fell into the well between the two platforms, receiving a shock. This experience apparently produced a convulsive seizure, and pyridoxine hydrochloride was prepared for use. However, the subject slowly got up and was forced by intermittent low amperage shock to climb to the work platform. During the ensuing work period, the subject evidenced almost total impairment on visual and auditory monitoring, approximately 50% impairment on the continuous and discrete avoidance tasks, and no further jumps were attempted throughout the 13 minute work period. Forty-two out of 72 possible shocks were received and at the completion of the work period, the subject would not jump back to the exit end of the Box. But when the transfer cage and Box doors were opened, the subject jumped the full distance perfectly and landed in the transfer cage. During the next work period at 1230, the subject would not jump after landing on the work panel side of the Box and was allowed to remain in front of the panel. During this work period performance was less impaired on continuous and discrete avoidance than at 1130, but was totally impaired on visual and auditory monitoring. A total of 37 out of 71 potential shocks were received. No significant signs of clinical illness were noted, but at 1330 performance was totally impaired on visual and auditory monitoring, and a slight impairment was noted on continuous and discrete avoidance and on gross motor

behavior. At 1430, visual and auditory monitoring were still totally impaired, but by 1630 (the ninth hour of testing) the subject had recovered and his performance was quite good. Only 2 shocks out of a possible 27 were received during the last 3-minute work period: one on continuous avoidance and one on visual monitoring. During this second UDMH test, a significant decrement ($p < .05$) on all performance tasks was found.

Subject #7

1st Control Test - The subject received the saline injection at 0730 and - except for two shocks received during the first work period on auditory monitoring, and one shock during the second work period on continuous avoidance - performed in the usual manner. Figure 4 provides a graphic presentation of the data for this control day and also the data which resulted from subsequent experimentation with this subject.

1st UDMH Test - The injection of UDMH was given at 0800 and there were no clinical signs of illness throughout the day of testing. A significant ($p < .05$) increment was observed in continuous avoidance behavior, and there was no impairment in any of the other tasks.

2nd Control Test - The injection of saline was given at 0730, and the only observation of interest for the day was that the subject failed to jump 5 out of 33 times and thus received 5 shocks. Overall performance was in line with previous control measures.

2nd UDMH Test - The subject was injected with UDMH at 0800, and at 1026 coughing and gagging occurred, followed by the expulsion of a small amount of frothy fluid. Performance at 1030 was unaffected. At 1120 the subject exhibited "dry heaves" and a small amount of frothy mucous was expelled. Performance at 1130 was most satisfactory; however, upon return to the home cage after this work period the subject once again gagged and expelled a small amount of frothy mucous. Performance at 1230 was still of a good

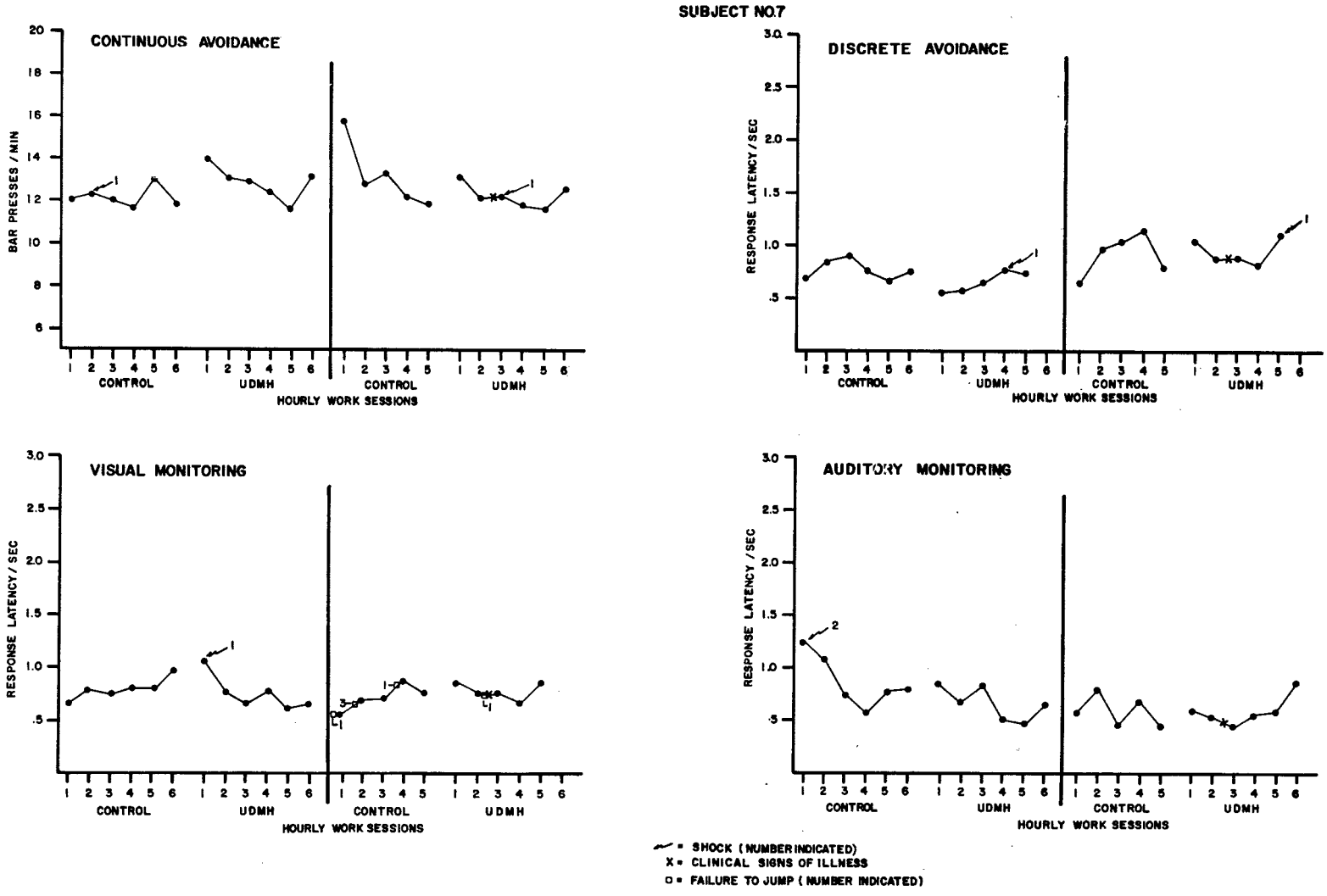


Figure 4. Control and Experimental Data (Subject 7)

quality, but upon return to the home cage the subject gagged and vomited more than at any previous time. Performance at 1330 was without incident and no further signs of clinical illness were noted. Recovery from the clinical illness (performance was never impaired) appeared complete by the end of the sixth hour of testing.

Subject #8

1st Control Test - The subject received the saline injection at 0730 and received only 1 shock (auditory monitoring) during the entire day. There were no significant observations. Figure 5 provides a graphic presentation of the data for this control day and also the data which resulted from subsequent experimentation with this subject.

1st UDMH Test - The UDMH injection was given at 0800, and no signs of clinical illness were exhibited during the day of testing. Although no significant behavioral changes occurred, four shocks (out of a possible 216) were received by the subject on continuous avoidance, 3 (out of a possible 54) on discrete avoidance and one shock was given for failure to jump during the fifth work period.

2nd Control Test - The saline injection was given at 0730 and, with the exception of one shock on discrete avoidance during the sixth work period, no clinical signs of illness or performance impairment occurred throughout the day of testing.

2nd UDMH Test - The subject was injected with UDMH at 0800 and there were no indications of difficulty until the 1130 work period. During the first two 3 minute performance sessions all tasks were performed well, but at the end of the second three minute work period the subject would not execute the jump required to place him on the side of the Box where the performance panel was located. Therefore, the subject was removed from the Box and returned to his home cage. At 1153 the subject was observed coughing and this was followed by a considerable amount of vomitus. At 1200 the subject lay

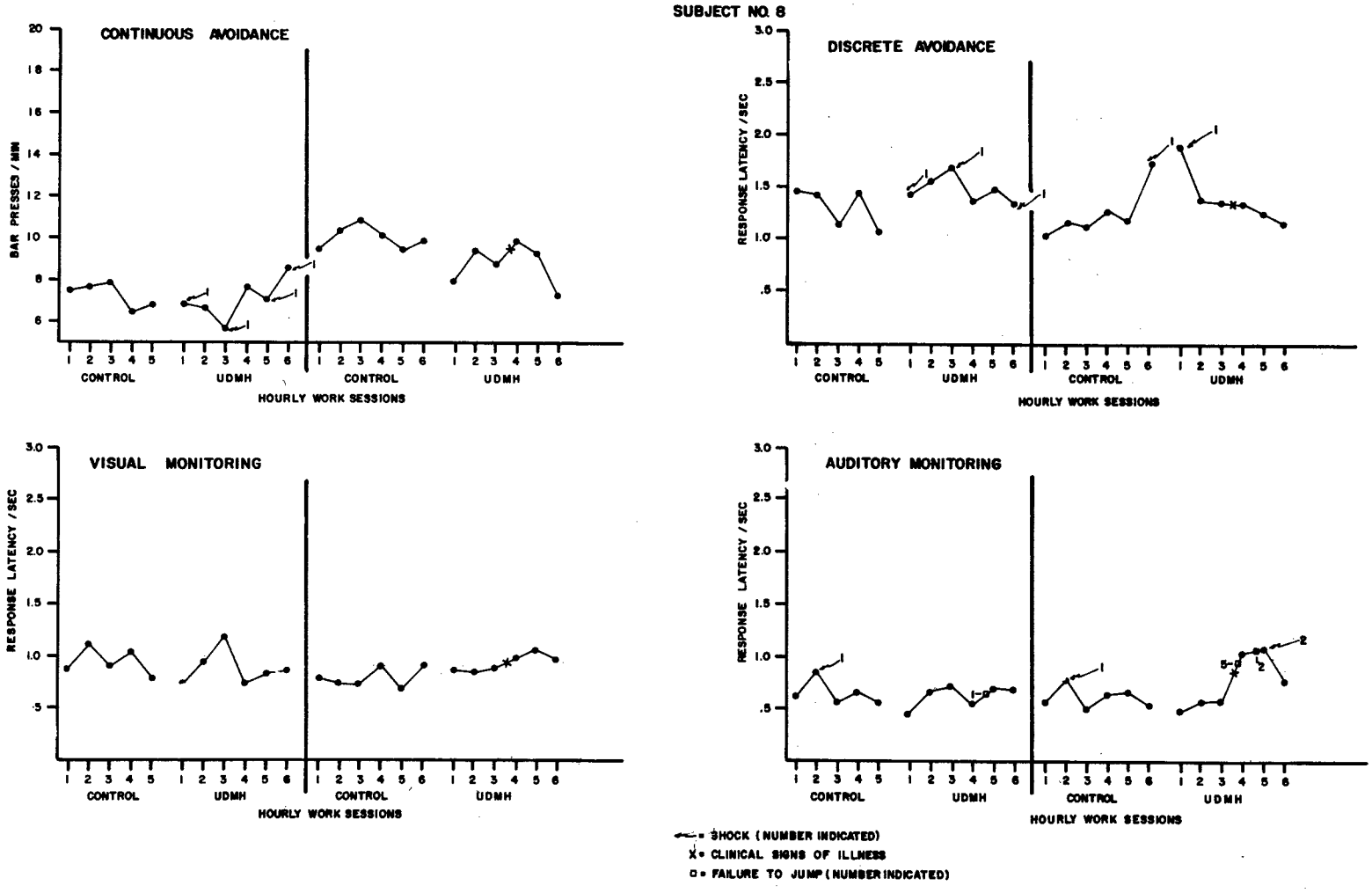


Figure 5. Control and Experimental Data (Subject 8)

quietly in his cage with his eyes open. A closer look by the experimenter led to the subject's jumping up and toward the experimenter with teeth bared. No signs of clinical illness were noted for the remainder of the day. Performance on continuous avoidance and visual monitoring were found to differ significantly ($p < .05$) from performance during the previous control test, and auditory monitoring reflected an impairment with the subject receiving two shocks out of nine potential ones during the fifth work period at 1230. When testing was completed at 1345 (end of sixth hour) the subject was fully recovered.

In summary, then, the following results were obtained:

1. On the first replication one of the four subjects exhibited clinical illness after 3-1/2 hours. On the second replication all four subjects exhibited clinical illness between 2 and 3-1/2 hours.

2. On the first replication one of the four subjects exhibited significant performance decrements after 3-1/2 hours, and on the second replication three of the four subjects exhibited significant performance decrements after 3-1/2 hours. Of the nine instances of performance decrement occurring during the two replications, seven are attributable to two subjects. Only two instances of a significant increment in performance occurred, one in one subject who showed no decrement at any time during testing, and the other in one of the two subjects responsible for the majority of decrements. At the same time as decrements on continuous and discrete avoidance occurred at the .01 level of statistical significance, the increment on auditory monitoring was taking place.

3. Seven of the nine instances of performance decrement occurred during the second replication, and the other two instances occurred in the first replication involved the same subject.

4. All subjects exhibiting a decrement in performance and/or exhibiting clinical illness recovered within the day of the experiment.

Statistical summary data for all subjects are presented in Tables III, IV, V and VI on the following pages.

TABLE III

Summary Statistics on Effect of UDMH on Continuous Avoidance Behavior
(Bar Presses/Minute)

	Subject 2		Subject 4		Subject 7		Subject 8	
Replication	1st	2nd	1st	2nd	1st	2nd	1st	2nd
Statistic								
Mean, Control	15.1	13.4	9.9	11.0	12.1	13.2	7.3	10.0
Mean, UDMH	11.8	9.5	10.5	8.0	12.9	12.2	6.8	8.8
Mean diff	3.3	3.9	.6*	3.0	.8*	1.0	.5	1.2
SE Mean diff	.72	.80	.40	1.05	.37	.71	.41	.44
t-ratio	4.58	4.88	1.50	2.86	2.16	1.41	1.20	2.73
Control n	7	5	5	5	6	5	5	6
UDMH n	7	5	5	5	6	5	5	6
Significance P < (two tail test)	.01	.01	N.S.	.05	.05	N.S.	N.S.	.05

* Increment in performance; other differences reflect a decrement.

TABLE IV

Summary Statistics on Effect of UDMH on Discrete Avoidance Behavior
(Response Latency/Seconds)

	Subject 2		Subject 4		Subject 7		Subject 8	
Replication	1st	2nd	1st	2nd	1st	2nd	1st	2nd
Statistic								
Mean, Control	1.19	1.29	.53	.53	.78	.91	1.33	1.22
Mean, UDMH	1.47	1.32	.64	1.19	.66	.94	1.49	1.40
Mean diff	.28	.03	.11	.66	.12*	.03	.16	.18
SE Mean diff	.09	.12	.08	.36	.06	.10	.10	.13
t-ratio	3.11	.25	1.38	2.20	2.00	.30	1.60	1.38
Control n	7	5	5	5	6	5	5	6
UDMH n	7	5	5	5	6	5	5	6
Significance P < (two tail test)	.01	N.S.	N.S.	.05	N.S.	N.S.	N.S.	N.S.

* Increment in performance; other differences reflect a decrement.

TABLE V

Summary Statistics on Effect of UDMH on Visual Monitoring Behavior
(Response Latency/Seconds)

	Subject 2		Subject 4		Subject 7		Subject 8	
Replication	1st	2nd	1st	2nd	1st	2nd	1st	2nd
Statistic								
Mean, Control	.92	.84	.55	.61	.79	.71	.94	.79
Mean, UDMH	.97	.89	.69	1.91	.75	.75	.87	.92
Mean diff	.05	.05	.14	1.30	.04*	.04	.07*	.13
SE Mean diff	.03	.04	.08	.52	.09	.054	.10	.05
t-ratio	1.67	1.25	1.75	2.50	.44	.74	.70	2.60
Control n	7	5	5	5	6	5	5	6
UDMH n	7	5	5	5	6	5	5	6
Significance P < (two tail test,	N.S.	N.S.	N.S.	.05	N.S.	N.S.	N.S.	.05

* Increment in performance; other differences reflect a decrement.

TABLE VI

Summary Statistics on Effect of UDMH on Auditory Monitoring Behavior
(Response Latency/Seconds)

	Subject 2		Subject 4		Subject 7		Subject 8	
Replication	1st	2nd	1st	2nd	1st	2nd	1st	2nd
Statistic								
Mean, Control	.86	.73	.53	.61	.86	.59	.63	.59
Mean, UDMH	.75	.77	1.28	1.91	.66	.53	.61	.76
Mean diff	.11*	.04	.75	1.30	.20*	.06*	.02*	.17
SE Mean diff	.04	.04	.35	.52	.12	.07	.14	.12
t-ratio	2.75	1.00	2.14	2.50	1.67	.86	.143	1.42
Control n	7	5	5	5	6	5	5	6
UDMH n	7	5	5	5	6	5	5	6
Significance P < (two tail test)	.05	N.S.	N.S.	.05	N.S.	N.S.	N.S.	N.S.

* Increment in performance; other differences reflect a decrement.

DISCUSSION AND CONCLUSIONS

Since three of the nine instances of performance decrement involved Subject #2, it should be noted that, while UDMH performance data does differ from the control data, performance following UDMH injection is well in line with the performance level of this subject prior to beginning experimentation. This suggests that the three instances of decrement are most likely due to a comparison with enhanced performance during the control period rather than being a decrement attributable to UDMH. Further credence is given to this hypothesis by the fact that during the time of two of the decrements (CA and DA) on the first replication, this same subject exhibited a significant increment on the auditory monitoring task, and showed virtually no change in his visual monitoring behavior.

With regard to the other six instances of decrement, which are attributable to Subjects 4 and 8, it is important that these all occurred during the second exposure to UDMH. If one were to disregard the decrements observed in Subject #2 because of the observed enhancement during control periods, then this would mean that every decrement observed in this study came about during the second replication. This suggests that repeated exposure to UDMH may be of some consequence from a behavioral point of view, and further work should be done to test the tenability of such an hypothesis.

When performance on each of the tasks is examined relative to associated clinical illness, the following is of interest:

Task	No Illness or Associated Performance Decrement	Illness, but no Associated Performance Decrement	Illness and Associated Performance Decrement
CA	3	1	4
DA	3	3	2
VM	3	3	2
AM	3	4	1
	12	11	9

As may be readily observed, the three columns total 32, which is the product of 2 exposures to UDMH for 4 subjects performing 4 tasks (2 x 4 x 4). These findings are important in that in 11 instances illness occurred and there was no performance decrement, but in every case (9) where a performance decrement occurred, there was also associated clinical illness. We may assume that while an individual may continue to perform adequately in 50% of the cases where clinical illness exists (11/20), there will always be clinical illness associated with performance decrements. Further, it seems clear that of the two manifestations of exposure to UDMH, clinical illness will appear sooner in the time sequence (by as much as one hour) than performance decrement - at least on the type of tasks involved in this study. Finally, it was observed in all instances where clinical illness and/or a performance decrement existed that the subject recovered within the day of the experiment.

In conclusion, following UDMH injection one may expect clinical signs of illness after two to three hours, a performance decrement or change after three to three and one-half hours, and recovery to the pre-experimental level between six and nine hours.

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there was also associated clinical illness in the form of hyperactivity, nausea, vomiting, or lethargy. One subject showed no impairment following the two UDMH injections, while another subject exhibited an impairment on all four tasks during the second replication; this suggests the range of individual reactivity to UDMH exposure, and that repeated severe exposure may cause serious decrement of performance. From these data, one may expect clinical signs of illness after 2 to 3 hours, a performance decrement or change after 3 to 3-1/2 hours, and recovery to pre-exposure level of functioning between six and nine hours.

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